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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/830,190	04/21/2004	Ananth Annapragada	27428-4	7714

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
11/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/830,190	ANNAPRAGADA ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/24/07 has been entered.

Claims and Previous Rejections Status

2. Claims 1-4,6-11 and 25-33 are pending in the application.

3. The rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

4. The rejection under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

5. The rejection under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al. (US 5,676,928) or Tournier et al. (US 6,217,849B1) in view of Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) is withdrawn.

6. The declaration under 37 CFR 1.132 filed 9/18/07 is acknowledged but is not relevant in view of the new grounds of rejection.

New Grounds of Rejection

The rejection under 35 U.S.C. 103(a) as being unpatentable over Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) in view of Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) or Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50) as stated in the office action mailed 8/24/07 has been modified due to the amendment.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4,6-11,25 and 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) in view of Payne et al. (US 4,744,989) and further in view of Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50; pages provided are numbered 1-8) or Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308).

9. Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) discloses a PEG and/or antibody substituted liposome which are long-circulating and target-specific (p76, paragraphs 2 and 3). The blood circulation time of the liposomes are improved by coating the surface with PEG by decreasing their opsonization and recognition by the liver (p76, paragraph 2). The targeting of liposomes to infracted myocardium is possible

since normal myocardial cells do not permit extracellular macromolecules, such as antimyosin antibody, to traverse the cell membrane but necrotic cardiomyocytes with disrupted membranes cannot prevent the antibody from interacting with myosin (p76, paragraph 1). The liposomes are prepared by mixing PC, cholesterol and a PEG-PE (p77, paragraph 3). The liposomes of the disclosure include small liposomes of size 120-150 nm. According to applicants declaration filed 9/18/07, the recitation of "incorporated" (liposomes are radioactively labeled with the radioactive element via liposome-incorporated chelating agent DTPA (p77, paragraph 4) is defined as the external attachment of the radiolabeled contrast agent outside of the liposome. Therefore, prior to incorporation of the radioactively labeled contrast agent the targeted, pegylated liposomes of the disclosure include small liposomes of size 120-150 nm (p77, preparation of liposomes). Torchilin et al. does not disclose the encapsulation of an iodinated contrast agents.

10. Payne et al. (US 4,744,989) discloses liposomes prepared from a combination of lipids (column 5, lines 64-65) and adjuvants, such as cholesterol where the mean size of the liposome can be controlled to suit the particular medicament, such as an iodinated contrast agent (column 6, lines 11-30) to be carried by the liposome (column 3, lines 31-33; column 4, lines 33-36; column 4, lines 59-62). The liposomes of the disclosure have a mean size from about 100 nm to 6 microns (column 4, lines 57-58). The size may be affected by the amount of phospholipids, the pH and hydration medium (column 5, lines 1-9). The method of preparing the liposomes includes subsequent removal of the unencapsulated material (column 6, lines 60-61).

11. Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50; pages provided are numbered 1-8) teaches of Iopromide-containing liposomes for enhancing CT imaging. The liposomes contain soy phosphatidylcholine (SPC), cholesterol, soy phosphatidylglycerol (SPG) (6:3:1 molar ratio) and 5 mol% DPSE-PEG2000 which are administered intravenously into a rat tail vein at a dose of 250mg I/kg (p3, paragraph 4) and show prolonged blood circulation with CT density differences above 70 HU (abstract; p2, paragraph 1). The CT blood pool imaging in a rabbit with DSPE-PEG liposomes show approximately 71ΔHU after 45 min (p5, paragraph 4; fig 6A-6D). Sachse et al. also discloses that the PEGylated lipid derivatives in the liposome membrane provides for potent increase in circulation times (p1, paragraph 2) as they avoid the mononuclear phagocytic system (MPS) and target to non-MPS organs.

12. Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) discloses a computed tomography enhancing iodinated liposome composition containing soy phosphatidylcholine (SPC), cholesterol and soy phosphatidylglycerol (SPG) (p303, last paragraph). The contrast enhancing liposomal agents have a mean diameter of 201 nm are used for prolonged blood-pool opacification upon intravenous injection of 300mg I/kg (p305, paragraphs 3 and 8; p306, fig 2) which encompass the compositions for enhancing contrast of the instant claims. The contrast enhancing iodinated liposome compositions of the disclosure are observed immediately after administration up to 60 min with a mean peak enhancement of in the aorta of approximately 90ΔHU (p305, last paragraph; p306, first paragraph).

13. At the time of the invention it would have been obvious to one skilled in the art to prepare targeted-pegylated liposomes of the size 120nm-150 nm (Torchilin et al.) and utilize/try them for the encapsulation of the iodinated contrast agents of Payne et al. as the liposomes of Payne et al. may also be 100 nm in size. Torchilin et al. teaches that the blood circulation time for PEG-LL (large liposomes) is less than that for PEG-SL (small liposomes) (p81, paragraph 1). The disclosures are drawn to the same products (liposomes) and the encapsulation of the contrast agents of Payne et al. into the liposomes of Torchilin et al. will have predictable results, as there are multiple factors for controlling the size of the liposomes. The substitution of different lipids as taught by Sachse et al. or Leike et al. for the lipids of Torchilin et al. is advantageous as they are well suited for CT blood-pool imaging with iodinated contrast agents (Leike et al. p303, paragraph 1). In the case of small liposomes, Torchilin et al. (p80, small liposomes) teaches that grafting of PEG to the liposome surface sharply increases the liposomal circulation time due to the interaction of the PEG with plasma proteins (p80, small liposomes). Furthermore, it is obvious to vary and/or optimize the amount of (compound) provided in the composition, according to the guidance provided by (reference), to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Response to Arguments

14. Applicant asserts that Torchilin et al. teaches a preparation of liposomes where the attachment of the radioactive tracer is on the outside of the liposome as opposed to encapsulated within.

15. Torchilin et al. does teach that prior to incorporation of the radioactively labeled contrast agent the targeted, pegylated liposomes of the disclosure include small liposomes of size 120-150 nm (p77, preparation of liposomes). The reference of Torchilin et al. was used to teach of the preparation of these small liposomes and not encapsulation of the contrast enhancing agents.

16. Applicant asserts that there in no motivation to combine Leike et al. and Torchilin et al. as the liposomes of Torchilin et al. may very well render Leike et al. compositions inoperable, and vice-versa.

17. It would be obvious to try/substitute the different lipids taught by Sachse et al. or Leike et al. for the lipids of the iodine agent containing/encapsulating liposomes of the combined disclosures of Payne et al. and Torchilin et al. as they are advantageous and suited for CT blood-pool imaging with iodinated contrast agents (Leike et al. p303, paragraph 1). Applicant assertion that the liposomes of Torchilin et al. **may very well render** Leike et al. compositions inoperable, and vice-versa is opinion and conjecture and does not eliminate the fact that it would be obvious to try the lipids of Sachse et al. or Leike et al. for their advantageous characteristics.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
November 13, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER